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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,658	09/27/2000	Daniel M.. Gorman	15631-005920US	5950

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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	17

DATE MAILED: 07/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/671,658	Applicant(s) GORMAN ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,6-9 and 11* is/are allowed.

6)☒ Claim(s) *10 and 14-27* is/are rejected.

7)☒ Claim(s) *12 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644, Technology Center 1600.

2. Applicant's amendment, filed 5/14/02 (Paper No. 15), is acknowledged.
Claims 4 and 5 have been cancelled.
Claims 11-27 have been added.
Claims 1-3, 6-7 and 10 have been amended.
Claims 1-3 and 6-27 are pending and under consideration in the instant application.

3. Sequence compliance: Applicant's Request, filed 5/14/02, to transfer sequence from parent application 08/989,362 is acknowledged. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. This Office Action will be in response to applicant's arguments, filed 5/14/02 (Paper No. 15). The rejections of record can be found in the previous Office Action (Paper No. 13).

It is noted that New Grounds of Rejection are set forth herein.

5. Claims 12-13 and 23-24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

An antibody or antigen binding fragment thereof that is conjugated to a detectable label is broader in scope than an antibody or antigen binding fragment thereof.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Applicant's amendment has obviated the previous rejection of claims 1-3 and 6-10 are rejected under 35 U.S.C. 112, second paragraph.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 10 and 14-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies or fragments thereof which specifically bind SEQ ID NO:2, does not reasonably provide enablement for antibodies or fragments thereof which specifically bind to

a) a substantially pure or recombinant 499E9 polypeptide exhibiting 100% sequence identity over a length of at least 12 contiguous amino acids to SEQ ID NO: 2 (e.g., claim 10a);
b) a fusion protein comprising "499E9 sequence" (e.g., claim 10c);
c) *a* polypeptide of SEQ ID NO:2 (claim 14);
d) a polypeptide that shares "a biological activity" with mouse 499E9 and at least about 60% identity with SEQ ID NO:2 (claim 15a); or
e) a polypeptide encoded by a nucleic acid which hybridizes and shares a "biological activity" with mouse 499E9 (claim 15b).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 5/14/02, have been fully considered but have not been found convincing.

Applicant argues that there is no undue experimentation required to make and use the instantly recited antibodies and antigen binding fragments thereof on the grounds that that the state of the art recognized that there was tolerance in antibody substitution of the antibody-antigen interface and that the same antibody can recognize different antigens.

This argument is addressed in the context of the application of the rejection of record to the newly added claims.

In the instances noted supra the claim language permits substantial variation in the amino acid sequence of the polypeptide recognized by the antibody. Claim 10a requires only that 12 unidentified contiguous residues be present in the context of any polypeptide sequence. There is no requirement that the antibody bind the 12 residues shared between the polypeptide of SEQ ID NO:2 and the polypeptide of claim 10a. Neither does there appear to be any direction given as to which contiguous 12 amino acids are shared.

Similarly, a fusion protein comprising a "499E9 sequence" as recited in claim 10c encompasses any fusion protein in which some undefined segment or homologus segment of 499E9 sequence is present. There is also no requirement that the antibody which binds the fusion protein bind the "499E9 sequence".

Likewise, the phrase "a polypeptide of SEQ ID NO:2" in claim 14 reads on subsequences of SEQ ID NO:2 since many polypeptides are encompassed in the full length of SEQ ID NO:2 (i.e., the indefinite article "a", as opposed to the definite article "the", reads on fragments of SEQ ID NO:2). Again, the spec

The recitation of percent identity language in claims 15a sand 25-27, as well as the hybridization language of claim 15b, also each permit substantial variation in the amino acid sequence of the polypeptide recognized by the antibody. While the claims do require that the variant polypeptide share some "biological activity" with the mouse 499E9; the claims do not recite what that "biological activity" is. Thus the only biological activity shared may be a non-specific biological activity such as immunogenicity.

Consequently, the instant claims permit the polypeptide recognized by the antibody to vary significantly in terms of structure and do not require the polypeptide to maintain any particular function.

However, the present specification fails to provide sufficient disclosure of such "variant" 499E9 polypeptides that maintain the structural and functional properties of the 499E9 polypeptide of SEQ ID NO: 2. The specification does not provide sufficient guidance as to which of the amino acids may be changed in 499E9 while still maintaining functional activity. Further, the specification fails to provide guidance as to the antibody epitopes in SEQ ID NO: 2 that results in antagonist antibodies that inhibit a particular function of the 499E9 polypeptide of SEQ ID NO:2. Without guidance as to the function of the polypeptide which is to be inhibited by the antagonist antibodies and the epitope of SEQ ID NO:2 that would serve as an antigen to elicit an antibody that would antagonize a particular function of the 499E9 polypeptide of SEQ ID NO:2; the experimentation left to the skilled artisan is in fact undue.

As previously noted, Coleman et al. (Research in Immunology, 1994; 145(1): 33-36, of record) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444, of record) teaches single amino acid substitutions **outside** the antigenic site on a protein effect antibody binding. Father, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991, of record) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li et al. (PNAS 77: 3211-3214, 1980, of record) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Thus it is highly unpredictable which polypeptide variants would maintain the relevant epitope that would elicit an antibody which could be used in methods of modulating function of the polypeptide of SEQ ID NO:2

The disclosure does not appear to identify the epitope, either linear or conformational, that must be present in a polypeptide before an antibody can be produced that would function as disclosed in the specification as filed with respect to a particular testable biological activity. Thus there is insufficient guidance as to how to make and use the instantly recited antibodies.

Applicant has argued that the state of the art recognized that there is tolerance in substitution of amino acids in the antibody-antigen interface and points to the Colman reference cited previously be the Examiner at page 33, last line for support.

The Examiner acknowledges that changes in the antibody-antigen interface can in some instances be tolerated - when it occurs in the CDRs of the antibody substitutions can even leads to an increase in affinity for the antigen. However, the instant variability is not in the antibody, it is in the antigen. In the absence of guidance as to the epitope of the antigen recognized by the antibody, the skilled artisan would have no basis for selecting certain amino acid residues for change. In addition, in the absence of a particular testable function to be maintained by the variant antigen, the skilled artisan would have no basis for using an antibody to the variant.

The scope of the claimed 499E9-specific antibodies is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of 499E9 polypeptides broadly encompassed by the claimed invention. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's or peptide's amino acid sequence, and, in turn, nucleic acid sequence, and still retain similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function.

However, the problem of predicting protein structure from mere sequence data of a limited number of proteins/nucleic acids and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Thus, applicant has not provided sufficient guidance to enable the skilled artisan to make and use of the claimed 499E9-specific antibodies in manner reasonably correlated with the scope of the claims broadly including a broad number of structural changes encompassed by the genus 499E9 as recited. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the 499E9 encoding nucleic acids and amino acids and still maintain biological activity or structural specificity of 499E9 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

10. Claims 10 and 14-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 5/14/02, have been fully considered but have not been found convincing.

Applicant argues that the combination of the disclosure of the species of SEQ ID NO:2 and the presence of "identifying characteristics" as set forth on pages 15-23 of the specification are sufficient to show that Applicant was in possession of the genus recited in instant claim 10.

This argument is addressed in the context of the application of the rejection of record to the newly added claims.

The specification discloses the polypeptide of SEQ ID NO:2 and methods of producing antibodies to SEQ ID NO:2 that modulate functions of the polypeptide of SEQ ID NO:2; therefore Applicant clearly is in possession of SEQ ID NO: 2 which comprises mouse 499E9.

However, instant claims 10 and 14-27 permit variation in the amino acid sequence of SEQ ID NO:2. The specification does not appear to establish which structural aspects of SEQ ID NO:2 should be maintained in order either to provide an antibody epitope, or to provide a functional polypeptide.

Contrary to Applicant's assertions, the specification at pages 15-23 simply provides possible methods of producing polypeptide variants. These methods do not identify which structure is an essential core structure that must be shared by all variants in order to convey any particular function.

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of antibodies which specifically bind variant polypeptides falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. See Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. Claims 1-3, 6-9 and 11 appear to be allowable.

12. Claims 12 and 13 would appear to be allowable if claim 12 were rewritten in independent form to obviate the objection set forth supra.

13. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
July 18, 2002

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